REMARKS

In the present amendment, the specification has been amended to correct a typographical error. This amendment is supported at page 46, lines 12-14 (which recites that the two antipodes of Compound 9 were separated) and the compounds provided in Table 1 (particularly Compounds 9, 22, and 25).

Claim 1 has been amended to further recite that "wherein said no activity is maintaining at least one of average normal bone density, average normal muscle mass, average normal reproductive function, and average normal libido seen in ugonadal warm-blooded male mammals, and wherein said agonist activity is having an activation effect greater than 5% in vivo as compared to control animals on the weights of at least one of ventral prostate, seminal vesicles, levator ani, and luteinizing hormone serum levels." This amendment to claim 1 is supported in the specification at page 6, lines 30-36. In addition, claim 25 has been added. The addition of claim 25 is supported by originally filed claim 1. After entry of the present amendments, claims 1-7 and 25 will be pending.

No new matter is believed to be added.

35 U.S.C. § 112, first paragraph

Claims 1-7 and 9 stand rejected as purportedly not being enabled by the specification. That rejection is respectfully traversed to the extent the rejection applies to the claims as amended herein.

Applicants direct the Examiner's attention to the compounds provided in Table 1 and the statement in the specification at page 45, lines 5-7 providing that "all of the exemplary compounds in the above Table [Table 1] demonstrated a SARM profile in accordance with the present invention." (Emphasis supplied.) Thus, it should be apparent that the specification teaches the 67 compounds of Table 1 as a representative sample of SARMs that exhibit antagonist activity in hormone-dependent tumor while exhibiting no activity or agonist activity against other, nontumor tissues containing the androgen receptor.

In addition, the Examiner's attention is directed to the description provided in the specification from page 45, line 8, through page 46, line 25, which merely summarizes the results obtained in testing the SARMs provided in Table 1.

The specification enables one of skill in the art to make and use the claimed methods, including the SARMs recited in the claimed methods. As recited on page 8, lines 13-15, various

methods for identifying SARMs having antagonist activity against hormone-dependent tumors while exhibiting no activity or agonist activity against other nontumor tissues containing the androgen receptor can be used. Such methods are taught throughout the specification, and were used to enable the actual, representative working examples provided in the specification.

In one embodiment, taught beginning at page 8, line 16, antagonist activity in hormone-dependent tumor is ascertained via screening for inhibition of growth, either *in vitro* or *in vivo*, in hormone-dependent tumor cell lines. In this embodiment, the agonist or antagonist activity of a potential SARM is also measured in a normal, nontumor cell line as taught beginning at page 9, line 6.

The specification also provides beginning at page 10, line 21, that SARMs having antagonist activity in hormone-induced tumors and no activity or agonist activity in other nontumor tissues can be designed using information about the AR crystal structure and the estrogen receptor crystal structure with estradiol, tamoxifen, or raloxifen. In this regard, the Examiner alleges in the Office Action at page 4, first complete paragraph, that due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation. Applicants note, however, that the specification provides the crystal structures at page 10, second complete paragraph:

> SARMs having antagonist activity in hormone-induced tumors and no activity, or more preferably agonist activity, in other nontumor tissues can also be designed using information about the AR crystal structure and the estrogen receptor (ER) crystal structure with estradiol, tamoxifen or raloxifen. The crystal structure of the androgen receptor ligand binding domain (AR-LBD) has been determined to 2.0 Å resolution and is described in U.S. Patent Application Serial No. 09/687,609, filed October 13, 2000 and corresponding PCT/US00/28495, Matias *et al., J. Biol. Chem.* **275**, 26164-26171 (2000) and Sack *et. al., Proc. Natl. Acad. Sci. USA* **98**, 4904-4909 (2001), herein incorporated by reference. The crystal structure of ER is disclosed, for example, in WO 99/50658, herein incorporated by reference. Using these crystal structures, structure-based or rational drug design techniques can be used to design, select, and synthesize chemical entities, including the inhibitory and stimulatory SARMs of the present invention.

Moreover, as provided in the specification at page 12, line 9, the computational methods of the invention are for designing SARMs using such crystal and three-dimensional structural information to generate synthetic ligands that modulate the conformational changes of the androgen receptor's LBD and/or the estrogen receptor's LBD. As recited in the specification at page 20, beginning at line 29, once a computationally designed ligand (CDL) is synthesized, it can be tested using assays such as those described in the specification to establish its activity as

an antagonist in hormone-dependent tumors and to assess its activity in other nonmalignant AR containing tissues.

Applicants submit that the claimed subject matter is supported by the disclosure in the application, in that the disclosure contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. In particular, the disclosure provides actual, representative working examples of the claimed invention, and provides sufficient information to allow one skilled in the art to practice the full scope of the claimed invention. Thus, it should be apparent that the specification enables one of skill in the art to make and use the claimed subject matter. Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103

Claims 1-7 and 9 stand rejected as purportedly being unpatentable over Thorpe et al., in view of Zhi et al. and Li et al. That rejection is respectfully traversed to the extent the rejection applies to the claims, as amended.

Applicants respectfully submit that the Examiner's position is incorrect. In particular, the paragraph bridging pages 8 and 9 of the Office Action argues:

> Applicants state the combination of Thorpe et al., Zhi et al., and Li et al. references do not provide the feature of instant claim 1 regarding a SARM and (i) exhibit antagonist activity inhibiting growth of said hormone-dependent tumor and (ii) exhibits no activity or agonist activity against other, nontumor tissues containing the androgen receptor. This statement is found unpersuasive as various passages in the prior art references support this concept. For example, Li et al. describe using compounds in combination with a selective androgen receptor modulator (SARM) to treat, stimulate, and increase muscle mass (agonist activity of the combination including the SARM) and reduce cachexia due to cancer as well as using anti-tumor agents (antagonist activity of the combination including the SARM) (see details in 35 U.S.C. rejection above). The "comprising" terminology recited in instant claim 1, line 2, is reasonably interpreted such that other compounds may be combined in the administering to a patient. (Emphasis supplied.)

It should be noted that Applicants' claimed invention, as amended herein, is directed to a method for inhibiting the growth of hormone-dependent tumor cells, wherein this method includes the feature of administering to a patient a SARM that has two particular features: exhibits antagonist activity inhibiting growth of said hormone-dependent tumor; and exhibits no activity or agonist activity against other, nontumor tissues containing the androgen receptor. Note that the SARM itself must have these two features, i.e., that the SARM itself exhibits antagonist activity

inhibiting growth of said hormone-dependent tumor; and exhibits no activity or agonist activity against other, nontumor tissues containing the androgen receptor. Claim 1, as amended, recites:

> 1. A method for inhibiting the growth of hormone-dependent tumor cells in a patient in need thereof, comprising administering to said patient a selective androgen receptor modulator in an amount effective therefor, wherein:
> said selective androgen receptor modulator exhibits antagonist activity inhibiting growth of said hormone-dependent tumor; and
> wherein said selective androgen receptor modulator exhibits no activity or agonist activity against other, nontumor tissues containing the androgen receptor,
> wherein said no activity is maintaining at least one of average normal bone density, average normal muscle mass, average normal reproductive function, and average normal libido seen in ugonadal warm-blooded male mammals, and
> wherein said agonist activity is having an activation effect greater than 5% in vivo as compared to control animals on the weights of at least one of ventral prostate, seminal vesicles, levator ani, and luteinizing hormone serum levels.

Applicants agree with the Examiner's statement on page 9 that the "comprising" terminology allows for the combination of the SARM with other compounds for administering to a patient. However, the claims still require that the SARM must have the recited features.

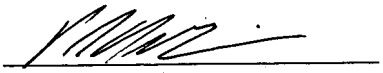
Thus, it should be apparent that the combination of Thorpe et al., Zhi et al., and Li et al. does not render obvious Applicants' claimed invention, and that the claims are patentable over this combination. Withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, allowance of the application is respectfully requested. The Examiner is invited to contact the undersigned if there are any questions concerning the prosecution of this application.

The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment.

Respectfully submitted,



Paul D. Golian
Attorney for Applicants
Reg. No. 42,591

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-4091

Date: September 27, 2004